REMARKS

The specification has been amended on Page 22, line 23, to correct the acronym for C-reactive protein from "CPR" to --CRP--. The use of "CPR" was an obvious error, as was acknowledged by the Examiner in the objection to the specification. (November 29, 2009 Office Action at 4.) It is also pointed out that the proper acronym, "CRP," is used in the specification on page 44, Table 44, and on page 45, line 13. The present amendment is consistent with this disclosure.

Claim 1 has been amended in the preamble and in step (c) to recite "detecting whether a patient has asymptomatic coronary artery disease as distinguished from those who do not have coronary artery disease...." Support is found in the specification at, for example, page 1, lines 17-19, page 11, lines 11-13, page 15, lines 21-22, page 19, line 26 to page 21, line 11, and page 47, lines 8-12.

Claim 22 has been amended to recite in the preamble, "for the medical professional to use in determining whether the individual has coronary artery disease as distinguished from those who do not have coronary artery disease..." and to recite in step (d) "for the medical professional to determine whether the patient has asymptomatic coronary artery disease as distinguished from those who do not have coronary artery disease...." Support is found in the specification at, for example, page 1, lines 17-19, page 11, lines 11-19, page 13, lines 3-5, page 15, lines 21-22, page 19, line 26 to page 21, line 11, and page 47, lines 8-12.

Claim 13 has been cancelled without prejudice. The Examiner is thanked for pointing out that claim 13 had become a "substantial duplicate" of claim 2. (Office Action at 9.)

Withdrawn claims 43-88 have been cancelled without prejudice. (For clarity, it is noted that claims 9-11, 14, 21, 30-32, 35, and 42 had previously been cancelled without prejudice.)

No new matter has been added.

The Examiner indicated that "[c]laims 1-8, 12-13, 15-20, 22-29, 33-34, and 36-41 were examined in light of the elected species of OxLDL as the atherogenic protein and of C-reactive protein as the acute phase reactant." (Office Action at 2.)

Applicant thanks the Examiner for the withdrawal of certain rejections. The Examiner's new ground of rejection under 35 U.S.C. § 103 is addressed below.

Information Disclosure Statement

The Examiner asserted that the Information Disclosure Statements ("IDS's") filed on November 8, 2007 and August 7, 2009 were not compliant with 37 CFR § 1.98(a)(1). (Id. at 3-4.) Although the Information Disclosure Statements were filed in accordance with longstanding accepted practice, the documents identified by the Examiner as not properly listed in the noted IDS's have been included in the Fourteenth Information Disclosure Statement submitted herewith and identified on Forms PTO/SB/08. It is also indicated in the accompanying IDS that the submission or listing of documents therein does not constitute an admission that any of the documents are "prior art" to the present application.

It is submitted that the accompanying IDS is proper and that all documents identified therein should be considered by the Examiner.

Objection to the Specification

The Examiner objected to the disclosure "on page 22, line 23, [because] 'CPR' should apparently read --CRP--." (Id. at 4.)

The specification has been amended to correct the acronym for C-reactive protein from "CPR" to --CRP--, as requested by the Examiner. Withdrawal of the objection is requested.

Obviousness Rejection

Claims 1-8, 12-13, 15-20, 22-29, 33-34, and 36-41 were rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Holvoet et al., U.S. Patent No. 6,309,888 ("Holvoet") in view of Valkirs et al., U.S. Publication No. 2003/0109420 ("Valkirs").

Holvoet concerns "a method having a clinically sufficient degree of diagnostic accuracy for detecting the presence of and for distinguishing between or among the non-acute and the acute stages of coronary artery disease for a human patient from the general population, the non-acute stage of coronary artery disease being either asymptomatic coronary artery disease or stable angina and the acute stages of coronary artery disease being unstable angina and acute myocardial infarction." (Col. 4, lines 6-14.) Holvoet indicates that "the method [comprises] performing step (b) and performing at least one of steps (a) and (c)[, wherein the steps

are]: a) testing a sample from the patient for a clinically significant presence of a first marker whose presence above a predetermined level can indicate with a very high degree of diagnostic accuracy the presence of coronary artery disease; (b) testing a sample from the patient for a clinically significant presence of second marker whose presence above a predetermined level can indicate with a very high degree of diagnostic accuracy the presence of an acute stage of coronary artery disease; and (c) testing a sample from the patient for a clinically significant presence of a third marker whose presence above a predetermined level can indicate with a high degree of diagnostic accuracy the presence of acute myocardial infarction." (Col. 4, lines 14-30.)

Holvoet also notes that "[t]he clinically significant presence (presence above a predetermined level) of the first marker (e.g., OxLDL having at least at least 60 substituted lysine residues per apo B-100 moiety) can indicate with a very high degree of diagnostic accuracy the presence of coronary artery disease." (Col. 5, line 64 to Col. 6, line 1.) In addition, Holvoet says that "[t]he clinically significant presence (presence above a predetermined level) of the second marker (e.g., MDA-modified LDL having at least at least 60 substituted lysine residues per apo B-100 moiety) can indicate with a very high degree of diagnostic accuracy the presence of an acute stage of coronary artery disease." (Col. 6, lines 15-20.) "The clinically significant presence (presence above a predetermined level) of the third marker (e.g., CK-MB or a troponin) can indicate with a high degree of diagnostic accuracy the presence of acute myocardial infarction." (Holvoet, Col. 6, lines 34-37.) "Use of the first and second tests (assays) together on a patient will allow the patient to be put with a clinically sufficient degree of

diagnostic accuracy into one of three categories: (1) having no coronary artery disease (first and second tests negative); (2) having coronary artery disease of the non-acute type, i.e., either asymptomatic coronary artery disease or stable angina (first test positive, second test negative); or (3) having coronary artery disease of the acute type, i.e., either unstable angina or acute myocardial infarction (both tests positive)." (Holvoet, Col. 6, lines 48-57.)

Valkirs concerns "methods for the diagnosis and evaluation of acute coronary syndromes. In particular, patient test samples are analyzed for the presence and amount of members of a panel of markers comprising one or more specific markers for myocardial injury and one or more non-specific markers for myocardial injury." (Abstract, lines 1-6.) Valkirs states that "[methods are provided] for the early detection and differentiation of stable angina, unstable angina, and myocardial infaction." (Abstract, lines 9-11.) Many and varied markers are named by Valkirs for possible use in testing for acute coronary syndrome. (See Paras. 53 to 101.) One of the markers named by Valkirs, which is characterized as a non-specific marker for myocaridial injury related to atherosclerotic plaque rupture, is malondialdehyde-modified low-density lipoprotein (MDA-modified LDL). (Paras. 79 and 84.) Other markers named by Valkirs, which are characterized generally as non-specific markers of myocardial injury, are "markers associated with inflammation and the acute phase response [including] C-reactive protein...." (Paras. 89-91.)

In making the rejection, the Examiner has asserted the following:

Holvoet et al. teach methods for detecting the presence of coronary artery disease by testing samples to determine the level of OxLDL, the level of MDA-modified LDL, and the level of a third marker such as troponin. See especially the abstract; column 1, lines 5-13; column 4, line 1 to column 8, line 45. OxLDL and MDA-modified LDL are atherogenic proteins as defined in the instant specification (page 21, line 22 to page 22, line 5).

Holvoet et al. further teach that OxLDL and MDA-modified LDL can be measured via immunological assays that employ the monoclonal antibodies mAb-4E6, mAB-IHll, or mAb-8A2 (column 4, lines 44-53; column 12, line 29 to column 15, line 33; column 17, lines 39-57; and the claims).

In addition to detecting the presence or absence of coronary artery disease (CAD), the methods of Holvoet et al. can also distinguish between non-acute CAD and acute CAD, where non-acute CAD means that the patient has either asymptomatic CAD or stable angina (column 3, lines 4-13; column 4, lines 1-15 and line 64 to column 6, line 66). These methods may be conducted as part of a screening or as part of a routine physical examination and may be performed on patients who are **asymptomatic** for coronary artery disease (see especially at column 6, lines 47-66).

It is noted that instant claim 1 recites "detecting whether the patient has asymptomatic coronary artery disease" (preamble and step (c)). As discussed above, Holvoet et al. make clear that their methods can be used to diagnose the absence of coronary artery disease, as opposed to the presence of non-acute coronary artery disease (either asymptomatic CAD or stable angina). As such, the methods of Holvoet et al. read on the claimed step of detecting *whether* the patient has asymptomatic CAD since in verifying that CAD is absent, the presence of asymptomatic CAD, stable angina, and acute CAD are being ruled out.

To assess whether marker levels in the patient samples are clinically significant, Holvoet et al. teach the use of predetermined cut points or threshold levels (i.e., cut-points), above which the markers are considered to be indicative of coronary artery disease. See column 4, lines 15-30; column 5, lines 7-63; column 19, lines 15-41; claim 1; and especially at column 8, line 42 to column 10, line 37 and at column 19, lines 33-40.

Holvoet et al. further illustrate measuring levels of C-reactive protein (see column 17, line 64 to column 18, line 2; column 19, lines 15-24; column 21, lines 61-62; column 22, lines 51-53; and Tables III and VI-IX), which is an acute phase reactant as disclosed instantly (specification, page 22, lines 22-23). Holvoet et al. observed that levels of C-reactive protein were elevated in subjects known to have various types of coronary artery disease as compared with control subjects (see Table III in particular).

Although Holvoet et al. thereby measured levels of the acute phase reactant C-reactive protein, this was apparently done as a means of validating the efficacy of OxLDL and MDA modified LDL as diagnostic markers, by comparison with other known markers such as C-reactive protein.

As such, the teachings of Holvoet et al. differ from the claimed invention in that the reference does not specifically teach using levels of an acute phase reactant as part of their methods to detect the presence, absence, and/or stage of coronary artery disease in a patient.

In addition, with respect to claim 22, Holvoet et al. fail to explicitly teach providing information to a medical professional as recited in the preamble and in steps (c)-(d).

However, it was known in the art at the time of the invention that measuring multiple markers of a disease in a "multimarker" approach may result in improved assay when performing clinical assays. For example, Valkirs et al. teach that a plurality of markers can be combined in a "multimarker" strategy to increase the predictive value of an analysis (diagnostic or prognostic) in comparison to that obtained using the markers individually [0017], [0107], [0184].

Therefore, because OxLDL, MDA-modified LDL, and C-reactive protein were all recognized by Holvoet et al. to be markers correlated with the presence and/or stage of coronary artery disease, it would have been obvious to one of ordinary skill in the art to also measure C-reactive protein levels and to use this information when detecting whether an asymptomatic patient has coronary artery disease according to the methods of Holvoet et al. In particular, it would have been obvious to also measure levels of C-reactive protein in asymptomatic subjects and to compare the observed levels with predetermined cut points or threshold levels in the same manner taught by Holvoet et al. for OxLDL and MDA-modified LDL, so as to assess the

presence, absence, and/or stage of asymptomatic coronary artery disease in the patient. Put another way, when detecting C-reactive protein in addition to OxLDL and MDA-modified LDL as part of the multimarker strategy of Valkirs et al., it would have been obvious to employ cut points for each marker being assayed (e.g., a first cut-point for OxLDL, a second cut-point for C-reactive protein, etc.) and to compare the subject's observed marker levels with these predetermined levels in the same manner illustrated by Holvoet et al. for their multimarker assay, in order to properly interpret the results of the assay.

One would be motivated to combine the reference teachings in this manner in order to improve the predictive value of the diagnostic assessment, based on the teachings of Valkirs et al. that a plurality of markers of a disease can be combined together to improve analysis as compared to the markers individually.

With respect to the steps of "providing information to a medical professional" as in claim 22, it is noted that Holvoet et al. discuss how their methods, which use multiple tests together, rapidly provide all the information needed by the clinician about the patient to permit possible life-saving treatment (column 6, line 48 to column 7, line 4; column 10, lines 38-63). The reference further discusses how a physician would use the results of the methods for diagnosis and treatment (ibid). For example, when the methods indicate that the patient has non-acute coronary artery disease, the physician may take action such as recommending a change in life style, prescribing appropriate medication, etc. (column 6, lines 48-66).

Therefore, although Holvoet et al. do not explicitly disclose a step in which the results of the method are provided to a medical professional to then use in determining whether the individual has coronary artery disease, the reference nonetheless clearly conveys that the results of their methods can be used by a physician in order to diagnose the presence, absence, and/or stage of coronary artery disease; as well as to administer appropriate treatment. When taken together with the general knowledge in the art, therefore, it would have been obvious to one of ordinary skill in the art to provide the results of the method of Holvoet et al. and Valkirs et al. to a physician so that the patient could be diagnosed and appropriately treated. For example, it would have been obvious to conduct the method in a clinical laboratory setting and to communicate the

> patient's test results to their physician in accordance with routine medical care practices.
>
> With respect to claims 3, 18, 24, and 39, Holvoet et al. teaches detection of OxLDL whose apo B-I00 moieties contain at least 60 substituted lysine residues (column 12, lines 55- 65).
>
> With respect to claims 6, 8, 15, 17, 19, 27, 29, 36, 38, and 40, which refer to detection of HDL as an anti-atherogenic protein, it is noted that Holvoet et al. also measured levels of HDL cholesterol (column 17, line 58 to column 18, line 6; and Tables III and V-IX). As such, it would have been further obvious to one of ordinary skill in the art to also measure HDL levels when performing the methods of Holvoet et al. and Valkirs et al., since the teachings of Holvoet et al. indicate that HDL is a marker that is normally measured when assessing coronary artery disease. In addition, it is noted that the data of Holvoet et al. demonstrate that HDL levels are correlated with the presence of coronary artery disease (Table III and column 20, lines 28-67). When taken together with the teachings of Valkirs et al. as discussed above, it would also have been obvious to measure HDL in addition to the markers discussed above when assessing subjects for the presence, absence, and/or stage of coronary artery disease. As above, one would be motivated to do this in order to improve the predictive value of the diagnostic assessment, based on the teachings of Valkirs et al. that a plurality of markers of a disease can be combined together to improve analysis as compared to the markers individually. [(Office Action at 4-9) (emphasis in original.)]

To forward prosecution in the present application, claim 1 has been amended to recite "[a] method of detecting whether a patient has asymptomatic coronary artery disease as distinguished from those who do not have coronary artery disease..." and "(c) detecting whether the patient has asymptomatic coronary artery disease as distinguished from those who do not have coronary artery disease...."

Also to forward prosecution in the present application, claim 22 has been amended to recite "[a] method for providing a medical professional with information

based on a sample obtained from a human patient who is asymptomatic for coronary artery disease for the medical professional to use in determining whether the individual has coronary artery disease as distinguished from those who do not have coronary artery disease..." and "(d) providing to the medical professional the appropriate one or more of the cut-points for the medical professional to determine whether the patient has asymptomatic coronary artery disease as distinguished from those who do not have coronary artery disease...."

It is well settled the Examiner bears the burden to set forth a *prima facie* case of unpatentability. *In re Glaug*, 62 USPQ2d 1151, 1152 (Fed. Cir. 2002); *In re Oetiker*, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992); and *In re Piasecki*, 223 USPQ 785, 788 (Fed. Cir. 1984). If the PTO fails to meet its burden, then the applicant is entitled to a patent. *In re Glaug*, 62 USPQ2d at 1152.

When patentability turns on the question of obviousness, as here, the search for and analysis of the prior art by the PTO should include evidence relevant to the finding of whether there is a teaching, motivation, or suggestion to select and modify the document(s) relied on by the Examiner as evidence of obviousness. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1731-32 (2007) (the obviousness "***analysis should be made explicit***" and the teaching-suggestion-motivation test is "***a helpful insight***" for determining obviousness) (emphasis added); *McGinley v. Franklin Sports*, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001). Moreover, the factual inquiry whether to modify document(s) must be thorough and searching. And, as is well settled, the teaching, motivation, or suggestion test "***must be based on objective evidence of***

record." *In re Lee*, 61 USPQ2d 1430, 1433 (Fed. Cir. 2002) (emphasis added). *See also Examination Guidelines for Determining Obviousness*, 72 Fed. Reg. 57526, 57528 (October 10, 2007) ("The key to supporting any rejection under 35 USC § 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious.").

Here, what the rejection should have done, but did not, was to explain on the record ***why*** one skilled in this art would modify Holvoet or Valkirs in the manner proposed by the Examiner to arrive at the claimed process. As is well settled, an Examiner cannot establish obviousness by locating documents which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force which would impel one skilled in the art to do what the patent applicant has done. *Takeda Chem. Indus., Ltd v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007) (citing *KSR*) (indicating that "it remains necessary to identify ***some reason*** that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound") (emphasis added); *Ex parte Levengood*, 28 USPQ2d 1300, 1301-02 (BPAI 1993). But this is precisely what the Examiner has done here. Thus, the rejection is legally deficient and should be withdrawn for this reason alone.

Beyond looking at the cited documents to determine if any of them suggests doing what the present inventor has done, one must also consider if the art provides the required expectation of succeeding in that endeavor. See *In re Dow Chem. Co. v. American Cyanamid Co.*, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988).

"Obviousness does not require absolute predictability, but a reasonable expectation of success is necessary." *In re Clinton*, 188 USPQ 365, 367 (CCPA 1976). Furthermore, the *U.S. Patent and Trademark Office Examination Guidelines* at page 57527 provide the following guidance to Examiners: "In short, the focus when making a determination of obviousness should be on what a person of ordinary skill in the pertinent art would have known at the time of the invention, and on what such a person would have reasonably expected to have been able to do in view of that knowledge." However, no such motivation or expectation of success can be found in the cited documents.

One skilled in the art would not reasonably have expected, based on the Examiner's combination of Holvoet and Valkirs, the success achieved in the method of claim 1 of detecting whether a patient has asymptomatic coronary artery disease as distinguished from those who do not have coronary artery disease, all of whom are asymptomatic, which comprises obtaining the level of an atherogenic protein, the level of an acute phase reactant, and optionally the level of an anti-atherogenic protein, obtaining at least one of the sets of cut-points recited in step (b)(i)-(vii), and detecting whether the patient has asymptomatic coronary artery disease as distinguished from those who do not have coronary artery disease based on at least one of the comparisons recited in step (c)(i)-(vii). One skilled in the art also would not have reasonably expected, based on Holvoet and Valkirs, the success achieved in providing a medical professional with information based on a sample obtained from a human patient who is asymptomatic for coronary artery disease for the medical professional to use in determining whether the individual has coronary artery disease as distinguished

from those who do not have coronary artery disease, as claimed in claim 22. The claimed methods provide significantly greater discrimination between patient populations than using a variety of single and combined markers, as is disclosed in the specification. One skilled in the art would not have had any suggestion or motivation to use the presently claimed method steps including use of the presently claimed markers. Nor would one skilled in the art have been able to predict the significant discrimination achieved with the claimed methods between those who have CAD and those who do not but all of whom are asymptomatic, in view of Holvoet, alone or in combination with Valkirs.

Initially, we note that Holvoet does not suggest, provide motivation, or provide any expectation of success in the claimed steps targeting a human patient who is asymptomatic for coronary artery disease in order to detect with significant discrimination whether the patient has asymptomatic coronary artery disease as distinguished from those who do not have coronary artery disease. Holvoet detects the presence of coronary artery disease and distinguishes between the stages of the disease with a clinically sufficient degree of diagnostic accuracy in human patients from the general population. (Abstract, lines 1-4.) The sample tested in accordance with the claimed methods is from a patient who is asymptomatic for CAD. Such a patient may have CAD but be asymptomatic, or such a patient may not have CAD, i.e., be healthy as to this disease. A population of patients who are asymptomatic can benefit from the claimed methods with regard to "significantly better discrimination between those who have ... [CAD] and those who do not but all of whom are asymptomatic." (Specification, page 15, lines 21-23.)

In no way does Holvoet suggest that the markers in accordance with the claimed methods could significantly distinguish between patients with no coronary artery disease and those with asymptomatic coronary artery disease, all of whom are asymptomatic. Holvoet notes the use of a marker that can indicate with a very high degree of diagnostic accuracy the presence of an acute stage of CAD, e.g., MDA-modified LDL, and at least one of a marker that can indicate with a very high degree of diagnostic accuracy the presence of CAD, e.g., OxLDL, or a marker that can indicate with a high degree of diagnostic accuracy the presence of acute myocardial infarction, e.g., a heart protein such as CK-MB or troponin. The Examiner points to no reason in Holvoet that would lead one skilled in the art to think that significant discrimination could be achieved in a method of detecting whether a patient has asymptomatic CAD as distinguished from those who do not have CAD, all of whom are asymptomatic, using an atherogenic protein and an acute phase reactant, as in the claimed methods. Furthermore, one skilled in the art would not have predicted that an atherogenic protein, an acute phase reactant, and anti-atherogenic protein would provide even further significant discrimination, as in the claimed invention.

Holvoet does not suggest the use of an acute phase reactant as presently claimed, which is a marker of systemic inflammation, in the claimed methods. While the Examiner did assert that Holvoet "illustrate measuring levels of C-reactive protein" and that Holvoet "observed that levels of C-reactive protein were elevated in subjects known to have various types of coronary artery disease as compared with control subjects (see Table III in particular)," the Examiner alleged that the measurement "was

apparently done as a means of validating the efficacy of OxLDL and MDA-modified LDL as diagnostic markers, by comparison with other known markers such as C-reactive protein." (Id. at 6.) The Examiner mischaracterizes Holvoet in alleging that measurement of C-reactive protein "was apparently done as a means of validating the efficacy of OxLDL...." Holvoet notes that "C-reactive protein is a marker of inflammation" (Col. 18, line 2), and that "C-reactive protein was found to be a marker of acute coronary syndromes [citations omitted]." (Col. 19, lines 20-24) (emphasis added.) Holvoet says Table V "shows the results of the simple logistic regression analyses for describing the ability of each of the parameters to distinguish individuals without coronary artery disease from those with coronary artery disease," in which the various parameters or markers listed are as follows: Total cholesterol, LDL, HDL, Total Chol/HDL chol. Ratio, Triglycerides, Oxidized LDL, and MDA-LDL. (Col. 20, lines 28-45.) Tellingly, C-reactive protein is not listed in Table V. In other words, Holvoet does not even consider C-reactive protein in terms of distinguishing individuals without CAD from those with CAD. Thus, Holvoet does not suggest, provide motivation, or provide any expectation of success in the use of an acute phase reactant in achieving discrimination, none the less significant discrimination, between individuals with CAD from those without CAD, all of whom are asymptomatic. We note that the Examiner correctly stated that "the teachings of Holvoet et al. differ from the claimed invention in that the reference does not specifically teach using levels of an acute phase reactant as part of their methods to detect the presence, absence, and/or stage of coronary artery disease in a patient." (Office Action at 6.)

Furthermore, the third marker used by Holvoet, which is used to determine the presence of acute myocardial infarction, is, generally speaking, a "heart protein," which is "a protein (e.g., an enzyme) that is produced as a result of or is otherwise associated with ischemic damage to the heart or that is a precursor or derivative of that protein." (Col. 12, lines 23-28.) Thus, Holvoet indicates the use of a heart damage-specific marker. Such a marker typically is released from the heart muscle and thus detectable only when there is ischemic damage. With regard to the use of an acute phase reactant, which is a marker of systemic inflammation, the specification indicates that "[e]levated levels of acute phase reactants are associated with a wide variety of diseases and conditions (e.g., infections with gram-positive and gram-negative organisms, rheumatoid arthritis, abdominal abscesses, multiple sclerosis, tuberculosis, burns, and patients with surgical trauma)." (Page 23, lines 10-13.) With regard to atherosclerosis, one skilled in the art would understand that systemic inflammation (which is detected from the use of the acute phase reactant) can occur in diseased or non-diseased individuals, and, thus, an acute phase reactant is neither an organ-specific nor a disease-specific marker. One skilled in the art could not have predicted that the claimed methods in which an atherogenic protein and an acute phase reactant and optionally an anti-atherogenic protein are used could achieve significant discrimination in detecting whether a patient has asymptomatic CAD as distinguished from those who do not have CAD, all of whom are asymptomatic.

Holvoet indicates that use of the first and second tests (assays) together on a patient, e.g., OxLDL and MDA-modified LDL, allows diagnosis with "a clinically

sufficient degree of accuracy" of those having no CAD and those having non-acute CAD which is either asymptomatic CAD or stable angina. (Col. 6, lines 48-55.) Table V and the accompanying text report that "the clinical presence of OxLDL above a predetermined level can indicate with a very high degree of diagnostic accuracy the presence of coronary artery disease as opposed to the absence of CAD." (Col. 20, lines 28-51.) The only other parameter reported in Table V that has any where near the diagnostic accuracy of OxLDL is MDA-modified LDL. Both of them are atherogenic proteins. MDA-modified LDL was found to be "below the minimum ... for a 'very high degree of diagnostic accuracy'" in characterizing the ability of each parameter to distinguish individuals without CAD from those with CAD. (Col. 20, lines 53-57.) In view of Holvoet's statements regarding the use of the two atherogenic markers that are specifically relevant to the disease process, OxLDL and MDA-modified LDL, one skilled in the art would not have predicted that the claimed methods using an atherogenic protein and an acute phase reactant and optionally an anti-atherogenic protein detect with significant discrimination whether a patient has asymptomatic CAD as distinguished from those who do not have CAD, all of whom are asymptomatic.

The use of multiple markers in Valkirs (which is entitled "Diagnostic Markers of Acute Coronary Syndromes and Methods of Use Therefor") for diagnosis of acute coronary syndromes provides no suggestion to one skilled in the art as to whether or not significant discrimination may be achieved in detecting whether a patient has asymptomatic CAD as distinguished from those who do not have CAD. Acute coronary syndromes (e.g., an acute myocardial infarction or unstable angina) are

clearly not asymptomatic CAD. Nor does Valkirs provide any suggestion or motivation as to how such improved detection as in the claimed methods could be achieved. There is no suggestion or motivation to use an atherogenic protein or an acute phase reactant, much less both in combination, optionally with an anti-atherogenic protein in the claimed methods of detecting whether a patient has asymptomatic coronary artery disease as distinguished from those who do not have coronary artery disease. Valkirs's use of MDA-modified LDL and markers associated with inflammation including C-reactive protein is for diagnosis of acute coronary syndrome ("ACS"). Valkirs refers to C-reactive protein in the category of "markers associated with inflammation and the acute phase response...." (Para 90, lines 6-8.) Valkirs notes that "[a]ctivation of the inflammatory response may be manifested in the early stages of ACS." (Para. 90, lines 1-2.) Association of the C-reactive protein with the acute phase of CAD leads one away from its use in the claimed methods.

Consistent with other statements noted above regarding CRP, Valkirs says that "[t]he concentration of CRP will be elevated in the plasma from individuals with any condition that may elicit an acute phase response, such as infection, surgery, trauma, and stroke." (Para. 91.) Valkirs also says that "[p]lasma has a high concentration of CRP and there is much variability in the reported concentration of CRP in the blood of healthy individuals." (Id.) This would lead one of skill in the art away from use of CRP to distinguish those with asymptomatic CAD from those without CAD, all of whom are asymptomatic. Moreover, one skilled in the art would not have expected to achieve significant discrimination as to whether a patient has asymptomatic

coronary artery disease as distinguished from those who do not have coronary artery disease, all of whom are asymptomatic, based on Valkirs's use of MDA-modified LDL and/or markers associated with inflammation and the acute phase response including C-reactive protein for use in diagnosis of acute coronary syndromes.

Furthermore, Valkirs does not disclose or suggest the use of cut-points as in the claimed methods. In fact, as indicated in the specification, the methods of the presently claimed invention have been applied to the clinical data reported in Holvoet and compared to use of the claimed methods. The results "[e]vidence the unexpected advantages of the present invention." (Page 38, lines 18-19.) See, for example, Table IV on page 44 in which values for the control, stable (chronic) angina population, and the acute coronary syndromes population are provided. The specification discloses that "[a]s will be understood by one skilled in the art, broadly speaking, for two given distributions, (e.g., one distribution or curve of negatives and the other of positives), if the means of two distributions are farther apart (all else being equal), there will tend to be less overlap of the two distributions. (Page 44, line 4 to Page 45, line 2). In comparing the distributions, for example, between the control group and "the Stable (Chronic) Angina sub-population," the specification discloses that the results "[indicate] a good separation between means and, therefore, less overlap." (Page 45, lines 3-7). Furthermore, the advantage over control is provided in Table IV for the stable (chronic) angina population and the acute coronary syndromes population. As the specification discloses, "[t]he separations achieved using the invention are far better than when any of OxLDL, C-reactive protein, or HDL is used alone." (Page 46, lines 16-17.)

Furthermore, the calculated advantage for (i) OxLDL x CRP, and (ii) OxLDL x CRP/HDL of the present invention are each significantly greater than comparison groups (a) to (e), which are as follows: (a) OxLDL; (b) CRP; (c) HDL; (d) CRP x Cholesterol; and (e) CRP x Cholesterol / HDL. (Page 44, Table IV; see also Page 47, lines 3-20.) Note in particular the improvement over OxLDL, the marker said by Holvoet to "indicate with a very high degree of diagnostic accuracy the presence of coronary artery disease." (Col. 5, line 65 to Col. 6, line 1.)

Although the control group of individuals is assumed to be "true negatives," the specification also discloses that "this is believed to be a conservative assumption because some of the control individuals, all of whom are asymptomatic, may in fact have [CAD]". (Page 44, lines 4-6.) The finding of good statistical separation between the "conservative" control group and diseased populations thus further supports the good separation and thus discrimination between the control and diseased groups.

The specification further discloses:

> In summary, the separation between the negatives (those in the Control sub-population) and the positives (those in either the Stable (Chronic) Angina or Acute Coronary Syndrome sub-population) is significantly greater when using the method of the invention (atherogenic protein plus acute phase reactant with or without anti-atherogenic protein) than when not using the invention (i.e., using Total Cholesterol plus C-reactive protein, or Total Cholesterol plus C-reactive protein plus HDL, or each of the three substances alone). ***These significant increases in separation are believed to sufficiently indicate the increased separation when using the method of the invention throughout the entire range of the disease,***

> ***including distinguishing those with asymptomatic coronary artery disease from those without coronary artery disease.*** [Page 47, lines 3-12 (emphasis added.)]

There would have been no expectation that the claimed methods, which use an atherogenic protein, an acute phase reactant, and an anti-atherogenic protein, would show a significant advantage over control (that is even greater than the advantage shown by the claimed invention's use of an atherogenic protein and an acute phase reactant). Although Holvoet notes testing HDL as a single parameter (as pointed out by the Examiner), Holvoet does not indicate the use of HDL in Holvoet's method of using a MDA-modified LDL with either OxLDL or a heart protein. One skilled in the art could thus surmise from Holvoet that HDL does not merit inclusion with the markers of Holvoet's reported methods. And, Valkirs is silent as to use of HDL.

A Marketing Brochure entitled "The Oxidized LDL Triple Marker Test: Taking Preventive Cardiology to a Higher Level," Shiel Medical Laboratory, 2009 (the "Brochure") is submitted herewith as Exhibit A (and it was previously submitted with the August 7, 2009 IDS; a copy is also provided with the accompanying IDS). As can be seen at the bottom of page 4 of the Brochure under the heading "REFERENCES," the last two lines, "United States Patent Application: 0050181451" is listed. The Brochure refers to the present application.[1]

[1] In referring to the present application, the Brochure would more accurately have recited US Patent Publication No. 20050181451. The Brochure also references "Harold M. Bates, Ph.D., of Shiel Medical Laboratory...." Harold M. Bates is the sole inventor of the present application.

The Brochure describes advantages of the commercially available Oxidized LDL Triple Marker Test. The Brochure indicates that the Oxidized LDL Triple Marker Test "[c]ombines and [i]ntegrates [t]hree [p]athophysiological [c]omponents of the [a]therosclerotic [d]isease [p]rocess with [t]hree [c]orresponding [i]ndependent [b]iomarkers...." (Page 2, lines 1-2.) The "[p]athophysiological [c]omponent[s]" are listed as atherogenesis, anti-atherogenesis, and inflammation, and the "[c]orresponding [b]iomarker[s]" are listed as oxidized LDL (OxLDL), high-density lipoprotein (HDL) and high sensitivity CRP (hs-CRP), respectively. (Page 2, table.) Thus, the Oxidized LDL Triple Marker Test of the Brochure is encompassed by the claimed methods in which an atherogenic protein, an acute phase reactant, and an anti-atherosclerotic protein are used. The Brochure also indicates that use of the Oxidized LDL Triple Marker Test "[i]dentifies [s]ignificantly [m]ore [p]atients with [c]oronary [a]rtery [d]isease [t]han [a]ll [o]ther [c]urrently [a]vailable [b]iomarker [t]ests." (Page 2, lines 5-6.) Furthermore, the Brochure says that "the [o]xidized LDL [t]riple [m]arker [t]est is the best discriminator between CAD and non-CAD patients." (Page 4, lines 1-2 and subsequent bar graphs.) The Brochure indicates advantageous results in the claimed methods using an atherogenic protein, an acute phase reactant, and an anti-atherosclerotic protein, and it evidences that these results translate to actual benefits for patients.

As is known in the art and as acknowledged by Holvoet, "coronary artery disease appears to be a multifactorial disease." (Col. 3, lines 58-59.) Workers in the field may have considered possible alternative ways to determine whether a patient who is asymptomatic for CAD in fact has asymptomatic CAD. Yet achieving methods

that provide significant discrimination in detecting whether a patient has asymptomatic coronary artery disease as distinguished from those who do not have coronary artery disease, all of whom are asymptomatic, as in the claimed methods, would not have been predictable to one of skill in the art. Here, known process options were not "finite, identified, and predictable," as in the facts presented in *KSR Int. Co. v. Teleflex, Inc.*, 127 S. Ct. 1727 (2007). Moreover, in *Abbott Labs. v. Sandoz, Inc.*, 89 USPQ 1161, 1171 (Fed. Cir. 2008), the Court of Appeals for the Federal Circuit indicated that the Supreme Court in *KSR* "did not create a presumption that all experimentation in fields where there is already a background of useful knowledge is 'obvious to try,' without considering the nature of the science or technology."

The Court of Appeals for the Federal Circuit has reaffirmed that "hindsight claims of obviousness" are improper. In distinguishing between fact patterns where a combination of known elements may or may not be proper, the Federal Circuit clearly articulated that simply varying all possible parameters until the claimed invention is arrived at in the absence of either an indication of which parameters to vary or an indication of which of many possible choices is likely to be successful is impermissible hindsight reconstruction. Indeed, the Federal Circuit concluded:

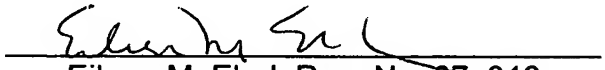
> Similarly, patents are not barred just because it was obvious "to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it." *Procter & Gamble Co. v. Teva Pharmaceuticals USA, Inc.*, 90 USPQ2d 1947, 1951 (Fed. Cir. 2009), *citing In re O'Farrell*, 853 F.2d at 903.

As in the *Abbott* case, one skilled in the art would not have anticipated success in achieving the presently claimed methods, which provide significant discrimination in detecting whether a patient has asymptomatic CAD as distinguished from those who do not have CAD, all of whom are asymptomatic, as "knowledge of the goal does not render its achievement obvious." *Abbott Labs. v. Sandoz, Inc.*, 89 USPQ at 1172 (affirming the district court's determination that Abbott is likely to prevail in its claim that the patent is valid, and upholding the grant of a preliminary injunction).

Clearly, the Examiner's rejection is based on impermissible hindsight reconstruction and is improper. Reconsideration and withdrawal of the rejection are requested.

For the foregoing reasons, entry of the amendments and allowance of the claims are requested. Issuance of a Notice of Allowance is respectfully requested. If the Examiner has any questions, please contact the undersigned.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on March 25, 2010.



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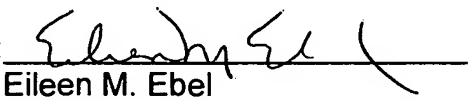
Respectfully submitted,

By: 

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